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頸部神経堤細胞の移動・分化を制御する Hoxa3 遺伝子の機能解析

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はしがき

本研究は、生存に重要な器官形成を司る Hoxa3 遺伝子の機能を詳細に解析したものです。かなりの部分は投稿中で、未発表ですが、発生生物学の教科書に記載されるべきデータを含んでいます。3年間で4回の研究場所の引っ越しなどを強いられる中、本研究費はこのような研究を支えるのにとても有用でした。ここに深く感謝致します。また、研究の大半を実際に行ってくれた元大学院生の（現カリフォルニア大学バークレー校研究員）五島一渡利夏子さんと北里大学医学部の亀田英子先生にも深く感謝の意を捧げたいと思います。

研究組織

研究代表者：千坂 修 （京都大学生命科学研究科助教授）

研究分担者：なし

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研究発表

（1）学会誌等

Kameda, Y., Arai, Y., Nishimaki, T., and Chisaka, O.
The Role of Hoxa3 Gene in Parathyroid Gland Organogenesis of the Mouse. Journal of Histochemistry and Cytochemistry 52, 641-651, 2004

Chisaka, O. and Kameda, Y. Hoxa3 Regulates the Proliferation and Differentiation of the Third Pharyngeal Arch Mesenchyme in Mice. Cell and Tissue Research 320, 77-89, 2005

（2）口頭発表 なし

（3）出版物 なし

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The Role of *Hoxa3* Gene in Parathyroid Gland Organogenesis of the Mouse

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SUMMARY While only a restricted number of the *Hoxa3* gene have effects on derivatives of the third branchial arch and pouch. To address the role of the *Hoxa3* gene in parathyroid organogenesis, we examined the third pharyngeal pouch development by immunohistochemistry (IHC) using the regulatory protein (SP-1) chromogranin A antibody, which recognizes the parathyroid fate as initial formation onward. At embryonic day (E) 12.5, the SP-1 chromogranin A immunoreactive primary rudiment of the parathyroid appeared in the cranial region of the third pharyngeal pouch of wild-type embryos. In *Hoxa3*-null mice, the third pharyngeal pouch was normally formed but failed to differentiate into the parathyroid rudiment, showing no immunoreactivity for SP-1 chromogranin A. Classical IHC using ultra-thin cameras have demonstrated that the ectoderm-derived neural crest cells are required for proper development of the pharyngeal pouch-derived organs, including the thymus and parathyroid glands. To visualize the migration and development of neuroectodermal neural crest cells in *Hoxa3* mutants, the heterozygotes were crossed with *lacZ* reporter mice in which *β-galactosidase* expression was specific to the neural crest cells. In *Hoxa3* heterozygotes and in wild types, ectoderm-derived neural crest cells heavily populated the pharyngeal pouches, including the third one, and surrounded the third pouch epithelium. These results indicate that loss of the *Hoxa3* gene affects the migratory ability of the third pharyngeal pouch to form the parathyroid rudiment and has no discernible effect on the migration of neural crest cells. *J. Histochem. Cytochem.* 52:641–651, 2004.

KEY WORDS
Hoxa3
parathyroid
thymus
neuroectoderm
SP-1 chromogranin A
immunohistochemistry
ultra-thin
camera

THE PARATHYROID GLANDS synthesize and secrete parathyroid hormone (PTH), which is essential for regulation of serum calcium concentration. The parathyroid cells and ducts originate develop from the third pharyngeal pouch in mice (Cowder and Hamburger, 1960). However, there is little information regarding parathyroid organogenesis during pharyngeal region development because of the lack of a specific marker that defines the rudiment. Three-dimensional reconstructions in hematoxylin–eosin-stained sections have been used to examine parathyroid development (Chen et al., 2001).

Chromogranin A, the major secretory protein of adrenal chromaffin cells, is a marker of the granular

chromogranin family of acidic glycoproteins that participate in the storage and secretion of peptide hormones and are expressed in many endocrine and neuroendocrine cells (O'Connor et al., 1983; Fischer-Collier et al., 1987; Winkler and Fischer-Collier, 1992). Calcitonin receptor 1 (SP-1) co-localizes with parathyroid hormone (PTH) in secretory granules of the parathyroid chief cells (Cohn et al., 1984). SP-1 and chromogranin A are chemically similar if not identical proteins (Cohn et al., 1982). The present study shows that SP-1 immunoreactivity appears in the parathyroid rudiment of the third pharyngeal pouch from the earliest stage of its organogenesis.

Hoxa3 belongs to the *Hox* family of transcription factors that play multiple roles in the segmental processes of neuroepithelial patterning (Krumlauf, 1994; Trautman and Krumlauf, 2000). In the *Hoxa3* homozygous null mutant mouse produced by gene targeting, the thymus and parathyroid glands derived from the

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